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Review Article

Evaluation of serum CEA for the gastrointestinal cancer diagnosis using different cut-off values

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Abstract: Background: Carcinoembryonic Antigen has been widely used in screening, diagnosis, therapeutic monitoring and prognosis evaluation of gastrointestinal cancer nowadays. It is disputable of the use of gastrointestinal cancer early diagnosis. The aim of our research is to find out the most suitable scale of cut-off value, based on the investigation of its impact on efficiency of CEA-indicated gastrointestinal cancer diagnosis. Methods: We searched PubMed, ISI Web of Science and Embase to identify research studies, and selected articles which focused their research on the sensitivity and specificity of CEA-based gastrointestinal cancer diagnosis. After calculating their Youden's index, resulting from the comparison of Youden's index variation among different cut-off values, we got the coordinated cut-off value with the greatest Youden's index to acquire the best cut-off value. Finding: After screening 2381 reports and meeting abstracts, we identified 9 eligible studies (published 2000-2015), involving 1103 cancer patients and 1425 healthy controls. When the range of cut-off value is between 2-3 ng/ml, the Youden's index is 0.43; when the range is between3-4 ng/ml, the Youden's index is 0.31; when the cut-off value reached 5 ng/ml, the Youden's index is 0.31; and when the range is larger than 6 ng/ml, the Youden's index decreased dramatically to 0.22. Interpretation: Given the result that Youden's index of CEA-based gastrointestinal cancer diagnosis is rather low when cut-off point is 5 ng/ml, whereas the same indicator is higher under the circumstance that cut-off value is 2-3 ng/ml, the better choice of cut-off value for CEA-based gastrointestinal cancer diagnosis is 2-3 ng/ml.

Keywords: Serum CEA, gastrointestinal cancer, cut-off values

Introduction

Gastrointestinal cancer refers to malignant conditions of the gastrointestinal tract (GI tract), gastric cancer and colorectal cancer are two most common types of which. Gastric cancer (GC) is a disease with high morbidity and mortality. Two-thirds of the GC cases occur in developing country. Among them, more than 40% of cases are located in China. Although GC has shown a significant decline in morbidity in recent years, but it still ranks second among all malignant tumors in China and the patients became more and more younger [1]. A total of 989,600 new GC cases and 738,000 deaths are estimated to have occurred in 2008, accounting for 8% of the total cancer cases and 10% of total deaths. Colorectal cancer is the third most commonly diagnosed cancer in males and the second in females, with over 1.2 million new cancer cases and 608,700 deaths estimated to have occurred in 2008 [2].

Since 1980s, tumor markers CEA are widely used in gastrointestinal cancer patients. CEA measurement is mainly used as a tumor marker to monitor colorectal carcinoma treatment, to identify recurrences after surgical resection, for staging or to localize cancer spread through measurement of biological fluids [3]. CEA levels may also be raised in gastric carcinoma, pancreatic carcinoma, lung carcinoma, breast carcinoma, and medullary thyroid carcinoma, as well as some non-neoplastic conditions like ulcerative colitis, pancreatitis, cirrhosis [4]. In terms of its lack of sensitivity, the CEA blood test is not reliable for diagnosing cancer or as a screening test for early detection of cancer [5].

It is commonly accepted to use 5 ng/ml as CEA cut-off value into screening, diagnosis, thera-

Table 1. Characteristics of Studies Included in the Meta-Analysis

Study, year	Primary lesion	Cancer patients	Healthy controls	Country
Yu JK, 2004	Colorectal	128	113	China
Fernandes LC, 2005	Colorectal	169	100	Brazil
Mroczko B, 2006	Colorectal	76	65	Poland
Lee H, 2008	Colorectal	129	53	Korea
Chen JS, 2010	Colorectal	232	365	China
Kobayashi Y, 2010	Stomach	74	106	Japan
He CZ, 2013	Stomach	149	235	China
Yang AP, 2014	Stomach	106	330	China
Thomas DS, 2015	Colorectal	40	58	UK

peutic monitoring and prognosis evaluation of gastrointestinal cancer. However, many researches revealed the relatively low sensitivity of CEA-based gastrointestinal cancer diagnosis, which leaded to a doubt of its value of screening and early diagnosis. The aim of our research is to find out the most suitable scale of cut-off value, based on the investigation of its impact on efficiency of CEA-indicated gastrointestinal cancer diagnosis. We analyzed different Youden's index coordinated with various cut-off values.

Materials and methods

Search strategy

A systematic literature search was performed in the electronic databases PubMed, ISI Web of Science and Embase until October of 2015. Search terms included 'CEA', 'Gastrointestinal tract or stomach or colorectal' and 'tumor, cancer, neoplasm or carcinoma'. The titles and abstracts of potential references were carefully scanned to exclude irrelevant articles. The remaining articles were evaluated to identify research that contained the topic of interest, and full texts were reviewed in depth afterwards.

Selection criteria

The studies included in the present research were randomized controlled studies that evaluated the association between the expression of CEA and gastrointestinal cancer diagnosis. Studies were included if they (1) focused on the diagnosis of gastrointestinal cancer; (2) provide cut-off values of serum CEA; and (3) analyzed the correlation of cut-off values of serum CEA with the diagnosis of gastrointestinal cancer. Articles were excluded on the basis of the following criteria: (1) Review articles or case reports; (2) The study is focused on animal models or cancer cells; (3) The study did not analyze the CEA expression and the diagnosis of gastrointestinal cancer; (4) The full text was unavailable.

Two of the authors (Dong-Ze Ji and Ze Zhang) independently screened the titles and abstracts of all identified studies. Studies that appeared to be relevant were selected, and the same two reviewers (Dong-Ze Ji and Ze Zhang) independently assessed the full-text versions. Disagreements were resolved by consensus or the involvement of a third reviewer (Hua-Guo Xu). **Table 1** shows the flowchart for selecting articles [6-14].

Data extraction

All data were extracted by two independent reviewers. Disagreements in data extraction were resolved by reaching a consensus in accordance with the original article. The following relevant data were extracted in a predefined table: author, year, country, primary lesion, cut off value, patient number, controls, case positive, case negative, control positive, control negative, sensitivity, specificity, Youden's index.

Statistical analysis

We made a scatter diagram (**Figure 2**) based on the relation between cut-off value and Youden's index, in which the horizontal axis is cut-off value and Youden's index is vertical axis. After having a preliminary link between cut-off value and Youden's index, we come up with a table (**Table 3**) according to 4 groups of cut-off values, respectively are 2-3 ng/ml, 3-4 ng/ml, 5 ng/ml, over 6 ng/ml. Last, we made a histogram (**Figure 3**) based on Youden's index, which are coordinated with 4 groups of cut-off values.

Results

Search results

A total of 2381 articles were retrieved using the search strategy (**Figure 1**). After the initial evaluation of the title and abstract, 2333 articles

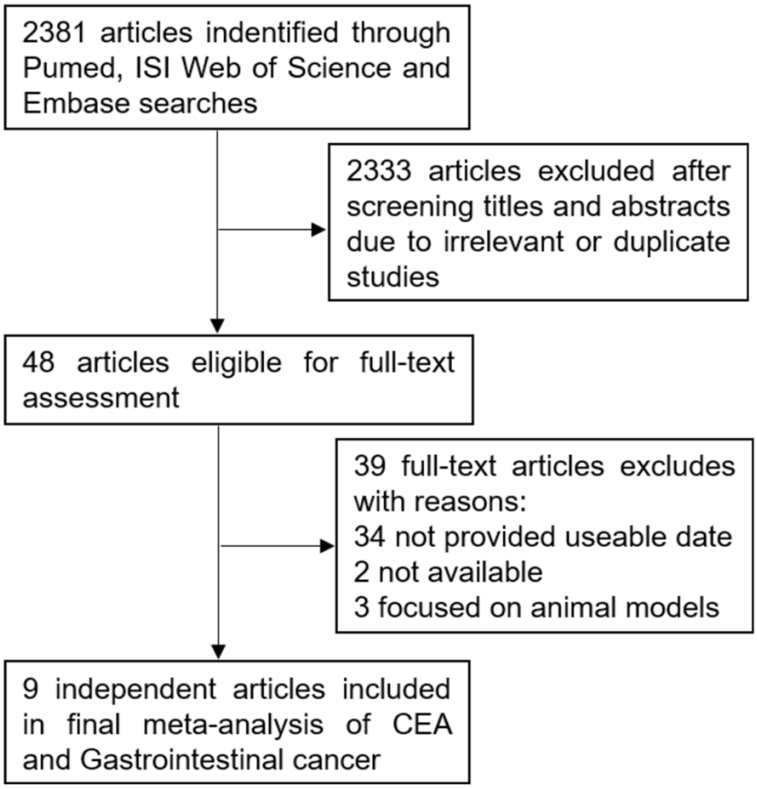

Figure 1. Flowchart of selection of studies for inclusion in meta-analysis. This flowchart shows the different steps of systematic review, starting from literature search to study selection and exclusion. At each step, the reasons for exclusion are indicated.

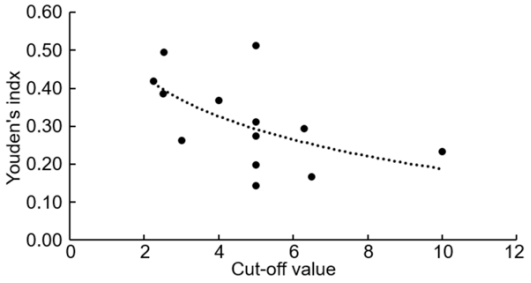

Figure 2. The relationship between the cut-off value and Youden's index. This scatter diagram is made based on the relation between cut-off value and Youden's index, in which the horizontal axis is cut-off value and Youden's index is vertical axis.

were excluded because of their irrelevance and duplication. The remaining articles were viewed in full text. Among the 48 articles, 39 were excluded, including 34 not provided useable date, 2 not available, 3 focused on animal models. Finally, 9 studies with 1103 cancer patients and 1425 healthy controls were included in the meta-analysis. All of the included studies evaluated CEA expression relevant to the diagnosis of gastrointestinal cancer.

Characteristics of eligible studies

All features of the 9 studies are listed in Supplemental **Table 1**. Among the studies, four originated from China, one from Japan, one from Korea, one from Brazil, one from Poland, one from United Kingdom. A total of 1103 cancer patients and 1425 healthy controls were included. Primary lesion in the colorectal was reported in 6 studies, and the Primary lesion in the stomach was reported in 3 studies. All studies showed the cut-off value of CEA-based gastrointestinal cancer diagnosis. Among them, two cases gave us the best cut-off value and three cases compared the efficiency of CEA-based gastrointestinal cancer diagnosis under different cut-off values.

Use different cut-off values of serum CEA for the gastrointestinal cancer diagnosis

Correlation results between cut-off values of serum CEA and the diagnosis of gastrointestinal cancer has been showed in **Tables 2** and **3**. Overall analysis showed that when the cut-off value is 5 ng/ml, which is commonly used, the specificity of CEA-based gastrointestinal cancer diagnosis reached 91.8%, but the sensitivity of it is 39.5%, with the Youden's index 0.31. However, when we range cut-off value between 2-3 ng/ml, though the specificity dropped to 79.3, the sensitivity dramatically increased to 63.7%, with the Youden's index 0.43. Moreover, when the cut-off value is larger than 6 ng/ml, the specificity raised to 98.5%, with the sensitivity 23.7%, and Youden's index 0.22.

Discussion

Carcinoembryonic antigen (CEA) describes a set of highly related glycoproteins involved in cell adhesion. CEA is normally produced in gas-

Table 2. Use different cut-off values of serum CEA for the gastrointestinal cancer diagnosis

Study, year	cut off value (ng/mL)	Case positive (n)	Case negative (n)	Control positive (n)	Control negative (n)	Sensitivity (%)	Specificity (%)	Youden's index
Yu JK, 2004	5	42	86	2	111	32.8	98.2	0.31
Fernandes LC, 2005	5	95	74	5	95	56.2	95.0	0.51
Mroczko B, 2006	4	28	48	0	65	36.8	100.0	0.37
Lee H, 2008	6.3	38	91	0	53	29.5	100.0	0.29
Chen JS, 2010	5	95	137	49	316	40.9	86.6	0.28
Kobayashi Y, 2010	5	12	62	2	104	16.2	98.1	0.14
He CZ, 2013	6.5	26	123	2	233	17.4	99.1	0.17
	2.24	87	62	39	196	58.4	83.4	0.42
Yang AP, 2014	10	27	79	7	323	25.5	97.9	0.23
	2.52	78	28	77	243	73.6	75.9	0.50
Thomas DS, 2015	5	10	30	3	55	25.0	94.8	0.20
	3	16	24	8	50	40.0	86.2	0.26
	2.5	23	17	11	47	57.5	81.0	0.39

Table 3. Different cut-off values ranges for the gastrointestinal cancer diagnosis

Cut off value (ng/mL)	Case positive (n)	Case negative (n)	Control positive (n)	Control negative (n)	Sensitivity (%)	Specificity (%)	Youden's index
2<n<3	188	107	127	486	63.7	79.3	0.43
3≤n≤4	44	72	8	115	37.9	93.5	0.31
5	254	389	61	681	39.5	91.8	0.31
n>6	91	293	9	609	23.7	98.5	0.22

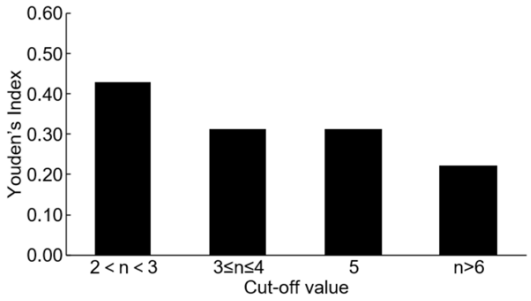

Figure 3. The relationship between the different cut-off values ranges and Youden's index. This histogram is made based on Youden's index, which are coordinated with 4 groups of cut-off values.

trointestinal tissue during fetal development, but the production stops before birth. Therefore, CEA is usually present only at very low levels in the blood of healthy adults. However, the serum levels are raised in some types of cancer, which means that it can be used as a tumor marker in clinical tests. This protein has been used for many years as a biomarker for gastrointestinal cancer, as well as other cancers. However, high serum CEA concentrations have been found in patients with other non-cancerous conditions, such as hepatitis, pancreatitis, inflammatory bowel disease, and obstructive pulmonary disease. In the present study, the prevalence of detection among all gastrointestinal cancer patients was 39.5% (254/643) using a CEA cut-off of 5 ng/mL, using a CEA cut-off of 2<n<3 ng/mL, the frequency of detection among gastrointestinal cancer patients with early stage cancer was 63.7% (188/295).

Because evaluating serum CEA has limited value in detecting early-stage gastrointestinal cancer [9], some researches tried to increase positive rate of gastrointestinal cancer with CEA combined other examinational methods. Some studies showed that combined use of AFP, CEA, CA125, CA72-4 and CAI9-9 improves the sensitivity for the early diagnosis of gastric cancer [12, 13]. Combined use of G-CSF and CEA improves the sensitivity for colorectal cancer. Combined detection using surviving autoantibodies and CEA produced better sensitivity (51.3%) and specificity (89.9%) compared to the sensitivity of CEA (40.9%) and the specificities of the individual markers (64.1% and 86.6%, respectively) [10]. Therefore, the posi-

tive rate of gastrointestinal cancer will be increased obviously, if using a CEA cut-off of 2<n<3 ng/mL combined other examinational methods.

Our study has limitations; caution should be used when interpreting our results because of the low number of studies. Screening asymptomatic population is different from screening among high-risk groups or of hospital-based screening by physicians. Although our study has limitations, the relationship between the cut-off value and Youden's index is stable. Thus, the better choice of cut-off value for CEA-based gastrointestinal cancer diagnosis is 2-3 ng/ml.

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Disclosure of conflict of interest

None.

Authors' contribution

Conceived and designed the experiments: JDZ XHG. Performed the experiments: JDZ ZZ. Analyzed the data: JDZ ZZ. Contributed reagents/materials/analysis tools: ZZ JDZ. Wrote the paper: JDZ ZZ XHG.

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References

[1] Jing JX, Wang Y, Xu XQ, Sun T, Tian BG, Du LL, Zhao XW and Han CZ. Tumor Markers for Diagnosis, Monitoring of Recurrence and Prognosis in Patients with Upper Gastrointestinal Tract Cancer. Asian Pac J Cancer Prev 2015; 15: 10267-10272.

[2] Jemal A, Bray F, Center MM, Ferlay J, Ward E and Forman D. Global cancer statistics. CA Cancer J Clin 2011; 61: 69-90.

[3] Duffy MJ. Carcinoembryonic antigen as a marker for colorectal cancer: is it clinically useful? Clin Chem 2001; 47: 624-630.

[4] Maestranzi S, Przemioslo R, Mitchell H and Sherwood RA. The effect of benign and malignant liver disease on the tumour markers CA19-9 and CEA. Ann Clin Biochem 1998; 35: 99-103.

[5] Duffy MJ, van Dalen A, Haglund C, Hansson L, Klapdor R, Lamerz R, Nilsson O, Sturgeon C and Topolcan O. Clinical utility of biochemical markers in colorectal cancer: European Group on Tumour Markers (EGTM) guidelines. Eur J Cancer 2003; 39: 718-727.

[6] Yu JK, Yang MQ, Jiang TJ, Zheng S. The optimal combination of serum tumor markers with bioinformatics in diagnosis of colorectal carcinoma. Zhejiang Da Xue Xue Bao Yi Xue Ban 2004; 33: 407-10.

[7] Fernandes LC, Kim SB, Matos D. Cytokeratins and carcinoembryonic antigen in diagnosis, staging and prognosis of colorectal adenocarcinoma. World J Gastroenterol 2005; 11: 645-8.

[8] Mroczko B, Groblewska M, Wereszczynska-Siemiatkowska U, Kedra B, Konopko M and Szmitkowski M. The diagnostic value of G-CSF measurement in the sera of colorectal cancer and adenoma patients. Clin Chim Acta 2006; 371: 143-147.

[9] Lee H, Rhee H, Kang HJ, Kim HS, Min BS, Kim NK and Kim H. Macrophage migration inhibitory factor may be used as an early diagnostic marker in colorectal carcinomas. Am J Clin Pathol 2008; 129: 772-779.

[10] Chen JS, Chen KT, Fan WC, Yu JS, Chang YS, Chan EC. Combined analysis of survivin autoantibody and carcinoembryonic antigen biomarkers for improved detection of colorectal cancer. Clin Chem Lab Med 2010; 48: 719-25.

[11] Kobayashi Y, Tajika M, Kawai H, Kondo S, Hara K, Mizuno N, Hijioka S, Sawaki A, Matsuo K, Nakagawa H, Nakamura Y, Yamao K. Serum tumor antigen REG4 as a useful diagnostic biomarker in gastric cancer. Hepatogastroenterology 2010; 57: 1631-4.

[12] He CZ, Zhang KH, Li Q, Liu XH, Hong Y, Lv NH. Combined use of AFP, CEA, CA125 and CAI9-9 improves the sensitivity for the diagnosis of gastric cancer. BMC Gastroenterol 2013; 13: 87.

[13] Yang AP, Liu J, Lei HY, Zhang QW, Zhao L and Yang GH. CA72-4 combined with CEA, CA125 and CAI9-9 improves the sensitivity for the ear-

ly diagnosis of gastric cancer. Clin Chim Acta 2014; 437: 183-186.

[14] Thomas DS, Fourkala EO, Apostolidou S, Gunu R, Ryan A, Jacobs I, Menon U, Alderton W, Gentry-Maharaj A and Timms JF. Evaluation of serum CEA, CYFRA21-1 and CA125 for the early detection of colorectal cancer using longitudinal preclinical samples. Br J Cancer 2015; 113: 268-274.